Pergamon

Life Sciences, Vol. 54, No. 10, pp. 641-644, 1994

0024-3205/94 $6.00 + .00

MINIREVIEW

IS MIGRAINE PROPHYLACTIC ACTIVITY CAUSED BY 5-HT_{2B} OR 5-HT_{2C} RECEPTOR BLOCKADE ?

Hans O. Kalkman

Preclinical Research Sandoz Pharma Ltd, Bldg 360-405, CH-4002 Basel, Switzerland

(Received in final form December 22, 1993)

Summary

It has been suggested that activation of 5-HT_{2C} receptors is involved in the initiation of a migraine attack. The 5-HT_{2C} receptor and the newly cloned rat fundus 5-HT_{2B} receptor show close pharmacological and structural resemblance. Antagonist pA_2 values from the rat stomach and pK_D values from a 5-HT_{2C} receptor binding assay correlated both highly significantly ($p<0.005$) with the daily dose of eight migraine prophylactic compounds. Although the small difference in antimigraine potency between the enantiomers of propranolol agrees with the lack of stereo-selectivity found on the rat fundus 5-HT_{2B} receptor but not with the 5-HT_{2C} receptor, the evidence available does not allow one to distinguish between 5-HT_{2C} and 5-HT_{2B} receptor blockade as possible mechanisms for prophylactic activity.

Fozard (1,2) has suggested that migraine prophylactic activity is caused by 5-HT_{1C} receptor blockade. His arguments are centered around the observation that a 5-HT_{1C} receptor agonist, mCPP (meta-chlorophenylpiperazine), provokes migraine (3), and the notion that most of the migraine prophylactic drugs are 5-HT_{1C} receptor antagonists. Recently two research groups succeeded in cloning the rat fundus 5-HT receptor (4,5). This newly cloned receptor displays remarkable structural and pharmacological similarity with the 5-HT_{1C} receptor. It was therefore of interest to challenge Fozard's theory and to test if blockade of receptors of the rat fundus type could explain a migraine prophylactic effect. According to a recent and accepted 5-HT receptor nomenclature both receptor subtypes are now considered as members of the 5-HT_2 receptor family (6). The 'classical' 5-HT_2 receptor has been renamed 5-HT_{2A}, the rat fundus receptor is referred to as 5-HT_{2B} and the 5-HT_{1C} receptor is now called 5-HT_{2C}. This nomenclature is used throughout the present article.

It is probable that a prophylactic effect against migraine attacks can be achieved via several pharmacological principles. I have concentrated on those compounds for which it is likely that their mode of action involves 5-HT receptor blockade (see for discussion 7). Eight such compounds were found (table 1). A vast literature exists about the rat isolated stomach fundus preparation and for all eight compounds at least one citation for a pA_2 value was found. Affinity

values (pK_D) for the 5-HT$_{2C}$ receptor were taken from radioligand binding experiments published by Hoyer (8) or from Hoyer (unpublished), using membranes from pig choroid plexus. The geometric mean of human daily dose (table 1) was then correlated with affinity for 5-HT$_{2B}$ (rat fundus *in vitro*) and 5-HT$_{2C}$ receptors (receptor binding experiments).

TABLE 1: Summary of Human Daily Dose, Antagonist Potency at 5-HT$_{2B}$ Receptor and Affinity for 5-HT$_{2C}$ Receptors

drug	reference	dose (mg/day)	log dose	5-HT$_{2B}$ (pA_2)	5-HT$_{2C}$ (pK_D)
methysergide	Whewell (20); Lance et al (21)	2-6	0.48	8.9-9.2	8.6
pizotifen	Lance et al (21)	4.5-9	0.78	7.5-8.0	8.1
Org GC 94	Sulman et al (22)	15	1.18	8.4	8.5
cyproheptadine	Lance et al (21)	12-24	1.23	7.5-8.4	7.9
mianserin	Monro et al (23)	30-60	1.62	7.3	8.0
amitriptyline	Gomersall & Stuart (24)	30-75	1.75	6.4	
chlorpromazine	Saper (25)	40-150	1.89	5.7-6.0	7.8
DL-propranolol	Widerö & Vigander (26)	80-320	2.23	6.1-6.5	6.2

For eight compounds with proven migraine prophylactic activity the effective dose range (mg/day), the logarithm of the geometric mean thereof, pA_2 values for blockade of 5-HT-induced contractions of the rat isolated stomach fundus and pK_D values for displacement of [^{3}H]mesulergine binding to pig choroid plexus, are given. pA_2 values are collected from different sources, while receptor binding data are from Hoyer (8 and unpublished).

Table 1 lists the eight compounds, the reference to the clinical study in which their activity was reported and the doses that were used. pA_2 values for methysergide (8.9), cyproheptadine (8.4) and chlorpromazine (5.7) are from (9). Schechter and Weinstock (10) reported a pA_2 value f 6.1 for D/L propranolol. A pA_2 value for amitriptyline (6.4) was taken from a publication by Wrigglesworth (11). The largest series of compounds was tested by Fischer et al (12). Th se authors reported the following pA_2 values: methysergide (9.2), cyproheptadine (8.0), pizotifen (7.5), mianserin (7.3), chlorpromazine (6.0) and D/L propranolol (6.3). Frankhuyzen and Bonta (13) found for cyproheptadine a pA_2 value of 7.5, whereas Clineschmidt et al (14) reported a value of 6.5 for D/L propranolol. Kalkman and Fozard (15) published pA_2 values for Org GC 94 (1,3,4,14b-tetrahydro-2,7-dimethyl-2H-dibenzo(b,f)pyrazino-(1,2-d)-(1,4)-oxazepine; 8.4), pizotifen (7.7), L-propranolol (7.0) and D-propranolol (6.6). In another study I obtained for pizotifen a value of 8.0 (Kalkman unpublished). The highest and lowest reported data are summarized in table 1. In the last column the affinities for the 5-HT$_{2C}$ receptor are listed. The correlation coefficient for the correlati n between log (geometric mean of the active human doses) and pA_2-values (5-HT$_{2B}$) amounted t -0.87 (low pA_2 values) and -0.89 (high pA_2 values). The c relation

between human dose and 5-HT$_{2C}$ receptor affinity had a correlation coefficient of -0.80. Spearman rank coefficients were -0.857 ($p=0.005$) and -0.929 ($0.005 > p > 0.001$) for 5-HT$_{2B}$ and 5-HT$_{2C}$, respectively.

It is remarkable that such high correlation coefficients were found between results from *in vitro* experiments in rat stomach and pig choroid plexus tissue and *in vivo* results in man. The antimigraine activity correlated slightly better with the 5-HT$_{2B}$ receptor affinity than with 5-HT$_{2C}$ affinity. However, considering the large differences in metabolism and drug distribution of the antagonists, this difference in correlation should not be given too much weight. The high degree of correspondence between inhibition of 5-HT-induced contraction in rat fundus and human antimigraine activity is, however, particularly noteworthy if one realizes that the data for the 5-HT$_{2B}$ receptor are collected from a wide variety of laboratories, whereas the data for the 5-HT$_{2C}$ receptor are homogeneous in that they stem from one laboratory only. In addition, with some antagonists prevention of 5-HT-induced contraction of the rat isolated stomach was not perfectly competitive, since higher concentrations of the antagonist reduced the maximum response. These confounding factors specifically affect the correlation with the 5-HT$_{2B}$ receptor.

There is one piece of evidence that supports the hypothesis that migraine prophylaxis is brought about by 5-HT$_{2B}$ receptors: Stensrud and Sjaastad (16) noted that D-propranolol (i.e. the enantiomer with the weaker ß-blocking effect) was as active as racemic propranolol in preventing migraine. The degree of stereo-selectivity of the propranolol enantiomers is clearly higher for the 5-HT$_{2C}$ receptor (ratio 5.3/6.8; ref 7 and Hoyer, unpublished) than for the 5-HT$_{2B}$ receptor (6.6/7.0; ref 15). The findings by Stensrud and Sjaastad (16) are thus more consistent with a 5-HT$_{2B}$ than with a 5-HT$_{2C}$ mechanism of action.

Inactive compounds: Ketanserin and pindolol are considered inactive as migraine prophylactic agents (17, 18). The affinity of ketanserin for 5-HT$_{2C}$ receptors is only 7.0, whereas its affinity for 5-HT$_{2A}$ receptors is 8.9 (8). In addition, Cohen and Wittenauer (19) reported that ketanserin did not antagonize 5-HT-induced contraction of the rat fundus in concentrations lower than 1 µM. Ketanserin can thus be considered a 5-HT$_{2A}$ receptor selective antagonist. Given the correlations established between human dose and 5-HT$_{2B}$ and 5-HT$_{2C}$ receptor affinity, one would not expect an effect of ketanserin at doses less than 100 mg/day. In agreement, Winther (17) found ketanserin (40 mg/day) inactive as a migraine prophylactic agent. Also pindolol (10 mg/day) is generally considered inactive in migraine prophylaxis (18). This, again, would have been predicted, since both at 5-HT$_{2B}$ (no antagonism in concentration below 10 µM; Kalkman unpublished) and at 5-HT$_{2C}$ receptors (pK_D 4.2; ref 8) the compound is extremely weak.

Agonists: 5-HT releasing agents like fenfluramine and reserpine are known to induce a migraine-like headache (for review see 2). The concept that migraine might be triggered by 5-HT$_{2C}$ receptor activation (1) was formulated after the observation by Brewerton et al (3) that the 5-HT$_{2C}$ receptor agonist, mCPP provoked migraine-like headaches. The peak plasma levels of mCPP that were reported by Brewerton et al (3) amounted to 1.8×10^{-7} M. In the rat isolated stomach fundus mCPP behaves as a potent (albeit partial) agonist with an EC_{50} value of 6×10^{-9} M (14). Thus, in concentrations which induce headache, mCPP not only stimulates 5-HT$_{2C}$ receptors (1,2), but also 5-HT$_{2B}$ receptors. The exact localization of the 5-HT$_{2B}$ or 5-HT$_{2C}$ receptors involved in this process remains, however, speculative.

Conclusion

Migraine prophylactic activity can be equally well ascribed to 5-HT$_{2B}$ as to 5-HT$_{2C}$ receptor

mechanisms. However, the lack of stereo-selectivity between the propranolol enantiomers favors the hypothesis that migraine can be prevented by 5-HT$_{2B}$ receptor blockade.

References

1. J.R. FOZARD, J.A. GREY, Trends Pharmacol. Sci. 10 307-309 (1989).
2. J.R. FOZARD, *5-hydroxytryptamine mechanisms in primary headache*, J. Olesen, P.R. Saxena (Eds) 200-212, Raven Press, New York (1992).
3. T.D. BREWERTON, D.L. MURPHY, E.A. MUELLER, D.C. JIMERSON, Clin. Pharmacol. Ther. 43 605-609 (1988).
4. M. FOGUET, D. HOYER, L.A. PARDO, A. PAREKH, F.W. KLUXEN, H.O. KALKMAN, W. STÜHMER, H. LÜBBERT, EMBO J. 11 3481-3487 (1992).
5. J.D. KURSAR, D.L. NELSON, D.B. WAINSCOTT, M.L. COHEN, M. BAEZ, Mol. Pharmacol. 92 549-557 (1992).
6. P.P.A. HUMPHREY, P.R. HARTIG, D. HOYER, Trends Pharmacol. Sci. 14 233-236 (1993).
7. J.R. FOZARD, *Advances in Neurology*, M. Critchley, A.P. Friedman, S. Gorini, F. Sicuteri (Eds) 33 295-307, Raven Press, New York (1982).
8. D. HOYER, J. Recept. Res. 8 59-81 (1988).
9. B.D. GÖRLITZ, H.H. FREY, J. Pharm. Pharmacol. 25 652-653 (1973).
10. Y. SCHECHTER, M. WEINSTOCK, Br. J. Pharmacol. 52 283-287 (1974).
11. S.J. WRIGGLESWORTH, Br. J. Pharmacol 80 691-697 (1983)
12. W. FISCHER, S. SCHUBERT, M. MÜLLER, Pharmazie 39 859-861 (1984).
13. A.L. FRANKHUYZEN, I.L. BONTA, Eur. J. Pharmacol. 25 40-50 (1974).
14. B.V. CLINESCHMIDT, D.R. REISS, D.J. PETTIBONE, J.L. ROBINSON, J. Pharmacol. Exp. Ther. 235 696-708 (1985).
15. H.O. KALKMAN, J.R. FOZARD, *Serotonin: molecular biology, receptors and functional effects*, J.R. Fozard, P.R. Saxena (Eds), 153-160, Birkhäuser, Basel (1991).
16. P. STENSRUD, O. SJAASTAD, Acta neurol. scand. 53 229-232 (1976).
17. K. WINTHER, Cephalalgia 5 (suppl 3) 402-403 (1985).
18. O. SJAASTAD, P. STENSRUD, Acta neurol. scand. 48 124-128 (1972).
19. M.L. COHEN, L.A. WITTENAUER, J. Pharmacol. Exp. Ther. 233 75-79 (1985).
20. J. WHEWELL, Br. Med. J. ii 395-398 (1966).
21. J.W. LANCE, M. ANTHONY, B. SOMERVILLE, Br. Med. J. ii 327-330 (1970).
22. F.G. SULMAN, Y. PFEIFER, E. SUPERSTINE, Arzneimittel Forsch. 31 109-112 (1981).
23. P. MONRO, C. SWADE, A. COPPEN, Acta psychiatr. scand. 72 (suppl 320) 98-103 (1985).
24. J.D. GOMERSALL, A. STUART, J. Neurol. Neurosurg. Psychiatry 36 684-690 (1973).
25. J.R. SAPER, J. Am. Med. Ass. 239 2480-2484 (1978).
26. T.E. WIDERÖ, T. VIGANDER, Br. Med J. ii 699-701 (1974).